

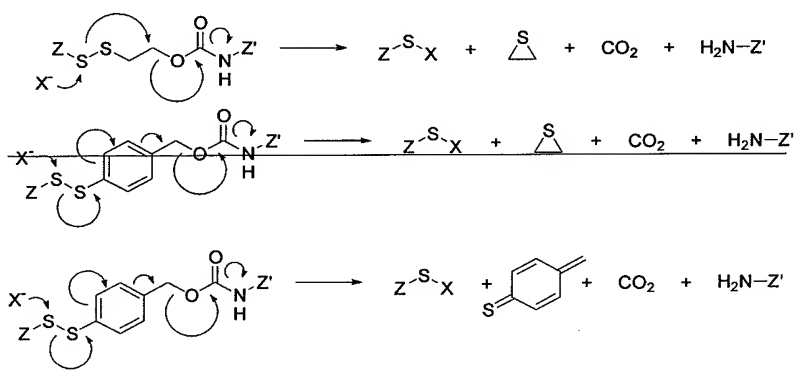
AMENDMENTS

IN THE SPECIFICATION

Under 37 C.F.R. § 1.121(b), please amend the specification as indicated below.

Please replace the paragraph on page 26 beginning at line 9 with the following paragraph.

Another illustrative mechanism for cleavage of bonds connected to or contained within releasable linkers, which may form part of the bivalent linker L, include the following beta-elimination and vinylogous beta-elimination mechanisms:



where X is a nucleophile, GSH, glutathione, or bioreducing agent, and the like, and either of Z or Z' is the vitamin, or analog or derivative thereof, or the drug, or analog or derivative thereof, or a vitamin or drug moiety in conjunction with other portions of the bivalent linker. It is appreciated that the bond cleavage may also occur by acid catalyzed elimination of the carbamate moiety, which may be anchimerically assisted by the stabilization provided by either the aryl group of the beta sulfur or disulfide illustrated in the above examples. In those variations of this embodiment, the releasable linker is the carbamate moiety.

On page 41 replace the paragraph beginning at line 9 with the following paragraph.

In one aspect, Z² can Z¹ can be a leaving group that allows attachment of the vitamin through a nucleophilic residue present on the vitamin, or analog or derivative thereof, such as an heteroatom, for example, nitrogen.

On page 41 replace the paragraph beginning at line 12 with the following paragraph.

In another aspect, Z^2 can ~~Z^+~~ can be a nucleophile, such as an heteroatom, for example, nitrogen, capable of displacing a leaving group present on the vitamin, or analog or derivative thereof, such as a carboxylic acid derivative, for example, an acid chloride.

On page 41 replace the paragraph beginning at line 16 with the following paragraph.

In another aspect, Z^2 can ~~Z^+~~ can be a precursor, such as a nitro group capable of being elaborated into a nucleophilic nitrogen via a reduction reaction, or an ester capable of being elaborated into an electrophilic acid chloride by sequential hydrolysis and chlorination. It should be appreciated that Z^2 can be an heteroatom linker.

On page 77 replace the paragraph starting at line 13 with the following paragraph.

Deacetylvinblastine monohydrazide (1 eq.) (*see* Barnett et al., *J. Med. Chem.*, **1978**, *21*, 88, the disclosure of which is incorporated herein by reference) was treated in fresh distilled THF with 1 eq. of trifluoroacetic acid. After stirring for 10 min the solution was treated with 1.05 eq. of N-(4-acetylphenyl)maleimide. Acyl hydrazone formation was completed in 45 min and the solvent was evaporated. The peptidyl fragment Pte-Glu-Asp-Arg-Asp-Asp-Cys-OH (0.85 eq.), prepared according to the general approach outlined in Scheme 12, was dissolved in water, and the pH was adjusted to 2.5 with 0.1 N HCl, causing the peptide to precipitate. The peptidyl fragment was collected by centrifugation, dried, and dissolved in DMSO. To the resulting clear yellow solution was added Hünig's base (15 eq.) and the acyl hydrazone ~~Michael~~ Michael adduct. After 1 h, the final conjugate was purified by HPLC.